

**Attachment C: FDA Statistical Review and Evaluation**

3854B1-03

## FDA Statistical Review and Evaluation

**Product:** Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein)  
**Indication:** Acute Otitis Media  
**Sponsor:** Wyeth-Lederle Vaccines

**Reviewer:** Jingyee Kou, Ph.D.

### Background:

Pneumovax was licensed for use in the United States on February 17, 2000 against invasive pneumococcal disease caused by the seven serotypes included in the vaccine. The sponsor is now pursuing the addition of an indication in the existing license of reducing otitis media caused by serotypes of *S. pneumoniae* included in the vaccine.

Two **randomized, double-blinded, cohort** studies were conducted: the FinOM study (D118-P809) was performed by the National Public Health Institute in Finland and the Kaiser study (D118-P8) was performed at Kaiser Permanente in Northern California. In addition, part of the FinOM Follow-up study results related to tympanostomy tube replacement is also included.

The FinOM study was originally designed to evaluate the efficacy of two heptavalent pneumococcal conjugate vaccines (Pneumovax and PncOMPC from Merck) against culture-confirmed pneumococcal acute otitis media due to vaccine serotypes, compared to a control vaccine, hepatitis B vaccine (HBV). Only data from Pneumovax and HBV are provided for this application.

The primary objective of the Kaiser study was to determine the protective efficacy of heptavalent pneumococcal conjugate vaccine against invasive disease due to serotypes included in the vaccine. One of the secondary objectives was to assess the effectiveness of vaccination on rates of acute otitis media and pneumonia in the study population as determined from computerized data sources.

The FinOM Follow-up study was designed to evaluate the long-term effects of Pneumovax on pneumococcal carriage and its serotype distribution, antibody persistence and otitis media morbidity. The tympanostomy tube placement is part of the study of the otitis media morbidity.

	FinOM (D118-P809)	Kaiser (D118-P8)
Number enrolled	1,662	34,146
Control	Hepatitis B (HBV)	Meningococcal group C Conjugate (MnCC)
Schedule	2, 4, 6, 12-15 mothss	2, 4, 6, 12-15 moths
Blinding	Double-Blind, Multi-center	Double-Blind
Case Definition	Myringotomy, cultures	Automated database search

### **FinOM Study**

#### **Primary endpoints:**

All episodes of acute otitis media (AOM) due to vaccine serotypes (VT) in per-protocol (PP) and intent-to-treat (ITT) populations

#### **Secondary endpoints:**

First and subsequent AOM episodes due to vaccine serotypes in PP population

#### **Other endpoints:**

- All AOM due to vaccine serotypes by dose in PP and ITT populations
- All AOM due to any pneumococcal (Pn) serotype in PP population
- All AOM with middle ear fluid (MEF) regardless of etiology in PP population
- All AOM regardless of etiology in PP population
- Recurrent AOM episodes

#### **Exploratory endpoint:**

All AOM due to individual vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and closely related serotypes (6A, 9N, 18B, 19A, 23A) in PP population

#### **Definition of episodes:**

An episode is defined as a clinic diagnosis of AOM at least 30 days from previous visit for AOM.

#### **Definition of frequent or recurrent AOM:**

A child was considered to have recurrent AOM if the child had 3 AOM episodes within a period of 6 months or 4 episodes within a period of 12 months.

**Definition of follow-up periods:**

**Per-protocol (PP):** Starts 14 days after the third injection and ends on the day of discontinuation as per-protocol or on the day of the close-out visit at the age of 24 months.

**Intent-to-treat (ITT):** Starts on the day the first dose was administered and ends on the day of permanent discontinuation or on the day of the close-out visit at the age of 24 months.

		HBV(N=831)	Prevnar(N=831)	Total(N=1662)
PP, N(%)	Completed	794 (95.5)	786 (94.6)	1580 (95.1)
	Included until discontinuation	27 (3.2)	25 (3.0)	52 (3.1)
	Excluded	10 (1.8)	20 (2.4)	30 (1.8)
ITT, N(%)	Completed	799 (96.1)	798 (96.0)	1597 (96.1)
	Included until permanent discontinuation	32 (3.9)	33 (4.0)	65 (3.9)

**Statistical Analysis method:**

The relative risk (*RR*) of AOM between the vaccine and control groups was estimated by using Cox proportional hazard regression model with Anderson-Gill counting method (Anderson & Gill, 1982). Vaccine efficacy (*VE*) is estimated as  $VE = 1 - RR$ . The within subject inter-dependency is accounted for by using the robust standard error estimates for the estimated regression parameters (Lin & Wei, 1989).

In Anderson-Gill counting process, each event is expressed as a separate record or one row in the data file, so one subject can have multiple records if the subject had multiple AOM episodes during the follow-up period. Each record contains an interval defined as (starting date, event date], where starting date is either 0 for the first day of follow-up or previous event date which the open parenthesis indicates is not included in the current time period. The event date could be the date of an AOM episode, the date the subject was terminated from the follow-up, or the closing date of the follow-up.

### Summary of results from FinOM study:

The efficacy estimates with Cox proportional hazards regression model, with a variable indicating whether a subject is in the vaccine group or the control group as the only covariate, are shown in table below.

			Number of episodes		Vaccine efficacy	
Endpoints	Type of episode	Follow-up	HBV	Prevnam	Estimate (%)	95% CI
Primary	VT	PP	250	107	57	44, 67
Primary	VT	ITT	292	135	54	41, 64
Secondary	VT-1 <sup>st</sup> episode	PP	177	89	52	39, 63
Secondary	VT-subsequent	PP	73	18	45	5, 69
Other	All Pn	PP	414	271	34	21, 45
Other	MEF	PP	1267	1177	7	-5, 17
Other	All AOM	PP	1345	1251	6	-4, 16

The following table lists the rates of AOM episodes due to vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), vaccine related (6A, 9N, 18B, 19A, 23A), other pneumococcal serotypes not in the previous two, in comparison with AOM caused by all pneumococcal serotypes in the PP population:

	Types of episodes	Number of episodes		Vaccine efficacy	
Endpoint		HBV	Prevnam	Estimate (%)	95% CI
Primary	VT	250	107	57	44, 67
Exploratory	VT related	84	41	51	27, 67
Exploratory	Not VT related	95	126	-34	-81, 0
Other	All Pn	414*	271*	34	21, 45

\*Not the sum of the first three numbers due to different counting process for VT and Pn described as follows:

VT: AOM due to vaccine serotypes is culture-confirmed pneumococcal AOM due to any of the serotypes included in Prevnam. A new episode starts if at least 30 days have elapsed since the beginning of the previous AOM due to the same serotype, or within any interval for different vaccine serotypes.

Pn: Culture-confirmed pneumococcal AOM. A new episode starts if at least 30 days have elapsed since the beginning of the previous pneumococcal AOM, irrespective of serotype.

### Baseline and other covariates:

A questionnaire on demographic information (gender, number of siblings and their age, parental education, duration of the pregnancy and birth weight) was completed at the first visit for each subject. A structured form with questions about known risk factors for AOM: breast-feeding, daycare status, smoking habits and recent antibiotic use, was filled out during each of the 8 scheduled healthy visits. The table below summarizes the covariates included in Anderson-Gill analyses in investigating the effects of the imbalance in baseline distribution after the study is unblinded. The sponsor concluded that there was no evidence to suggest significantly different vaccine effect in different populations defined by these factors.

		HBV		Pevnar	
Number randomized	Characteristics	831		831	
Gender	Male	428	(51.5%)	435	(51.5%)
AOM prior to enrollment	Yes	39	( 4.7%)	27	( 4.7%)
Gestational age	< 37 weeks	53	( 6.4%)	41	( 4.9%)
Birth weight	< 2.5 kg	42	( 5.1%)	25	( 3.0%)
Daycare attendance	6 months of age	8	( 1.0%)	8	( 1.0%)
	12 months of age	115	(13.8%)	144	(17.3%)
	18 months of age	247	(29.7%)	289	(34.8%)
Breast-feeding	< 6 months	376	(45.2%)	370	(44.5%)
Household smoking	Reported at ≥ 1 visit	291	(35.0%)	305	(36.7%)

The number of antibiotics prescribed during ITT follow-up was also provided in summary table:

	Total number of courses during ITT follow-up		Mean* ± SD Number of courses per subject during ITT follow-up		p-value
	HBV(N=831)	Pevnar(N=831)	HBV	Pevnar	
AOM treatment	2018	1940	2.43 ± 2.60	2.33 ± 2.65	0.164
AOM prevention	300	299	0.36 ± 0.94	0.36 ± 0.98	0.531
Other purposes	177	195	0.21 ± 0.51	0.23 ± 0.54	0.471
Regardless of purpose	2342	2277	2.82 ± 3.10	2.74 ± 3.14	0.275

\* Mean and SD of the whole treatment group including children who did not have any prescriptions.

**Sponsor's conclusions:**

- The Prevnar vaccine was found to be 57% efficacious against AOM caused by vaccine serotypes as compared to the control vaccine.
- The reduction is 34 % for all culture-confirmed pneumococcal AOM irrespective of serotype and 6% for AOM regardless of etiology.

**Kaiser Study****Primary endpoint:**

Overall incidence of AOM episodes in the PP follow-up

**Secondary endpoints:**

- Overall incidence of AOM episodes in ITT follow-up
- Risk of at least one episode
- Risk of frequent AOM
- Tympanostomy tube placement
- Overall incidence of AOM visits

**Exploratory:**

- Ruptured eardrums due to pneumococcal infection (in order to increase sample size for this purpose, the follow-up on ruptured eardrums did not end until November 6, 1998.)
- More severe cases of recurrent AOM

**Definition of episodes:**

An episode is defined as a clinic diagnosis of AOM at least 21 days from previous visit for AOM or at least 42 days if the visit appointment was made > 3 days in advance.

**Definition of frequent or recurrent AOM:**

A child was considered to have recurrent AOM if the child had 3 AOM episodes within a period of 6 months or 4 episodes within a period of 12 months.

**Definition of follow-up periods:**

**Per-protocol (PP):** Starts 14 days after the third injection and ends either when the child dropped out due to the health plan, the child became 16 months of age without receipt of the 4<sup>th</sup> dose, or until April 30, 1998 (database cut-off date).

**Intent-to-treat (ITT):** Starts on the day the first dose was administered and ends on April 30, 1998 or the death of the subject.

**Summary of results from Kaiser study:**

			Number of episodes		Vaccine efficacy	
Endpoints	Type of episode	Follow-up	MnCC	Prevnam	Estimate (%)	95% CI
Primary	All AOM	PP	17405	16124	7.0	4.1, 9.7
Secondary	All AOM	ITT	27199	25590	6.4	3.9, 8.7
Secondary	≥ 1 episode	PP	7411	7126	5.4	2.3, 8.4
Secondary	≥ 1 episode	ITT	10394	10112	4.9	2.3, 7.5
Secondary	Freq. AOM	PP	1809	1647	9.5	3.2, 15.3
Secondary	Freq. AOM	ITT	2839	2612	9.2	4.3, 13.9
Secondary	Tube placement	PP	198	157	20.3	1.8, 35.4
Secondary	Tube placement	ITT	240	192	2.06	4.0, 34.3

**Sponsor's conclusion:**

- The reduction for all episodes of AOM is 7%.
- There is a 20.3% reduction in the tympanostomy tube placement.

### **FinOM Follow-up study:**

Data from a post-marketing follow-up FinOM study were also analyzed to provide the efficacy estimate for tympanostomy tube placement. Analyses were performed in two populations:

1. Analysis Population 1: children enrolled in the FinOM follow-up study (N=756). Cases of tube placement were obtained from parents then ascertained through hospital or private physician office records.
2. Analysis Population 2: all children enrolled in the original efficacy trial and confirmed to be living in the same area in which the trial was conducted (N=1490 as of June 11, 2001). Case ascertainment was limited to a record search of hospital records.

	HBV	Pprevnar
Number of subjects	353	403
Gender (% Male)	51.3	49.1
Age range (ycars)	4.1 – 5.7	4.1 – 5.7

### **Summary of the tympanostomy tube placement follow-up study:**

Population	Period	Number of events		Vaccine efficacy	
		HBV	Pprevnar	Estimate (%)	95% CI
Population 1	Efficacy	95	95	12	-17, 34
Population 1	Follow-up	57	40	39	4, 61
Population 2	Efficacy	189	178	4	-19, 23
Population 2	Follow-up	92	53	44	19, 62

### **Sponsor's conclusion:**

- Pprevnar vaccine given at 2, 4, 6, and 12 months of age showed a long-term effect of 39% to 44% reduction in tympanostomy tube procedures during the period of 24 months to 4 to 5 years of age.
- Little reduction in the incidence in tube placement during the efficacy trial period was thought to be due to easy access to surgery for study participants.

### Reviewer's comments:

- Results from the FinOM study have been verified by the reviewer. For the Kaiser study, only the primary endpoint and the tube replacement results have been verified. However, no significant discrepancy in the analyses is expected.
- Cox proportional hazard regression model is a commonly used method of analysis for time-to-event data. The model assumption of proportional hazards was checked by graphical method, and Nelson-Aalen plots of cumulative hazard on a log scale were provided. The model assumption of proportional hazards appears to have been met.
- The individual baseline information provided to CBER as fixed covariates are: gender (male/female), AOM events prior to enrollment (yes/no), birthing weight ( $< 2.5$  kg /  $\geq 2.5$  kg), gestation age ( $< 37$  weeks /  $\geq 37$  weeks), and breast-feeding ( $\geq 26$  weeks /  $< 26$  weeks). The effects of the fixed covariates were verified by the reviewer. However, the effects of the time-varying covariates obtained at scheduled visit (age 2, 4, 6, 7, 12, 13, 18, or 24 months) including breast-feeding, daycare attendance and smoking in household will be verified at a later date.
- Although the Anderson-Gill method assumes that the events are independent of each other, it still gives a reliable estimate of the overall effect of treatment. However, it tends to underestimate the variance for the estimated parameter due to ignoring the within subject inter-dependency. Therefore, a robust variance estimating procedure for the estimated regression parameters developed by Lin & Wei (1989) was used. This robust variance has been shown to be robust to several possible misspecifications in the Cox model including the lack of proportional hazards, incorrect functional form of the covariates, and omitted covariates (Therneau & Grambsch, 2000). Since all important covariates were not prospectively identified, it is reasonable to assume a missing covariates case.
- The FinOM Follow-up study was not a randomized trial. Therefore, since selection bias cannot be ruled out, the results may best be viewed as supportive rather than conclusive.

### References:

- Anderson, P.K. & Gill, R.D. 1982. Cox's regression model for counting processes: a large sample study. *Annals of Statistics*, 10:1100-20.
- Lin, D.Y. & Wei, L.J. 1989. The robust inference for the Cox proportional hazards model. *Journal of the American Statistical Association*, 84:1074-1078.
- Therneau, TM & Grambsch, PM. 2000. Modeling Survival Data – Extending the Cox Model. Springer-Verlag, New York